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Publication date:
2018

Document Version
Peer reviewed version

[Link back to DTU Orbit](#)

Citation (APA):
Mazzoni, C., Tentor, F., Antalaki, A., Jacobsen, R. D., Mortensen, J., Slipets, R., Ilchenko, O., Keller, S. S., Nielsen, L. H., & Boisen, A. (2018). *Distribution and quantitative analyses of poorly water soluble drugs loaded by supercritical CO₂ impregnation in microcontainers with different sizes*. Abstract from Controlled Release Society Annual Meeting & Exposition 2018, New York, New York, United States.

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Distribution and quantitative analyses of poorly water soluble drugs loaded by supercritical CO₂ impregnation in microcontainers with different sizes

Chiara Mazzoni, Fabio Tentor, Anastasia Antalaki, Rasmus Due Jacobsen, Jacob Mortensen, Roman Slipets, Oleksii Ilchenko, Stephan Sylvest Keller, Line Hagner Nielsen, Anja Boisen

The Danish National Research Foundation and Villum Foundation's Center for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN), Department of Micro- and Nanotechnology, Technical University of Denmark, Ørstedes Plads 345C, 2800 Kgs. Lyngby, Denmark

Learning objectives:

1. Explain the supercritical CO₂ impregnation as a loading technique for microcontainers
2. Evaluate if the loading process is affected by the surface area exposed to the supercritical CO₂
3. Discuss if the quantity and distribution are different when loading two different poorly water soluble drugs

Introduction: Microcontainers (MCs) are polymeric cylindrical microdevices with only one side open [1]. MCs can be filled with a polymer matrix followed by loading a drug into the polymer-filled MCs using supercritical CO₂ (scCO₂) impregnation for potential use in oral drug delivery [2].

The aim of this study was to investigate the quantity, distribution and solid state form of the poorly water soluble drugs, ketoprofen and naproxen loaded into three different sizes of polymer-filled MCs using scCO₂. The different diameters of the MCs provided different surface areas of polymer exposed to the scCO₂ during the drug loading process.

Methods: MCs were fabricated in SU-8 (Fig. 1a) using two-steps of photolithography resulting in cylinders with internal diameter of 110 µm (small), 220 µm (medium) and 440 µm (large). MCs were filled manually with polyvinylpyrrolidone (PVP) K10 powder. Polymer-filled MCs were impregnated with ketoprofen or naproxen by means of scCO₂ impregnation (Fig. 1b). Ketoprofen was loaded using 100 bar, 40°C for one hour as scCO₂ impregnation parameters, whereas for naproxen, the parameters were set at 120 bar and 45°C for one hour. The *in vitro* release of ketoprofen and naproxen from the impregnated MCs was analyzed in 10 mM PBS solution at 37°C using a µDISS profiler. For evaluation of the solid state form of the drugs in the MCs for the different sizes, Raman spectroscopy and X-Ray Powder Diffraction were used. Raman maps were acquired using a DXR Raman microscope to analyze the distribution of the drug in the MCs.

Results: The quantity of the drug loaded into the different sizes of MCs and for the two drugs was not found to be statistically different. The release of naproxen or ketoprofen from the MCs showed similar kinetics for the different sizes and for the two drugs, reaching 90 % release within the first 10 min. By the use of Raman microscopy, it was evaluated if the exposed surface area influenced the distribution of the drugs in the MCs. An example with ketoprofen can be seen in Fig. 2, where the distribution of the drug in the uppermost layers inside the MCs was evaluated. Ketoprofen loaded into the MCs was found to be in its amorphous form, whereas naproxen was in a metastable form.

Conclusions: MCs having different surface areas exposed to the scCO₂ did not affect the quantity and release kinetics of loaded ketoprofen or naproxen.

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ACKNOWLEDGEMENTS: The authors would like to acknowledge the Danish National Research Foundation (DNRF122) and Villum Fonden (Grant No. 9301) for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN).

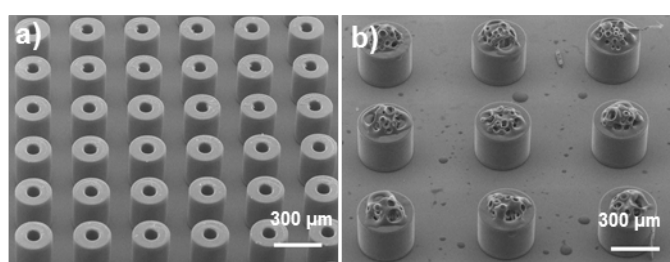


Fig. 1: SEM images of a) small empty MCs and b) ketoprofen-loaded medium MCs.

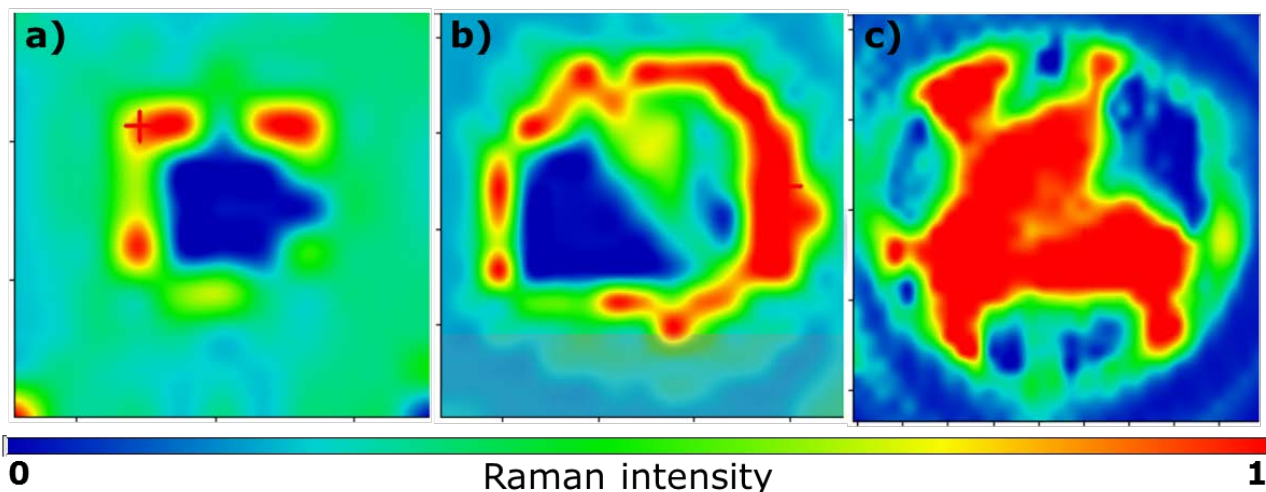


Fig. 2: Raman map on peak 1003 cm⁻¹ representing the distribution of ketoprofen in the uppermost layers inside the of a) small, b) medium and c) large MCs.